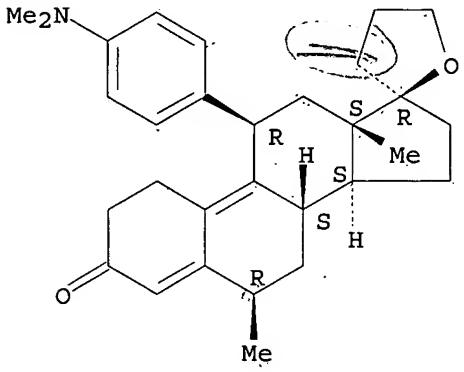
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 118968-41-5 REGISTRY
CN Spiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, 11-[4-(dimethylamino)phenyl]-4',5'-dihydro-6-methyl-, (6.beta.,11.beta.,17.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[17H-cyclopenta[a]phenanthrene-17,2'(3'H)-furan], spiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one deriv.
OTHER NAMES:
CN **Org 31710**
FS STEREOSEARCH
MF C30 H39 N O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMINFORMRX, DDFU, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, MEDLINE, PHAR, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



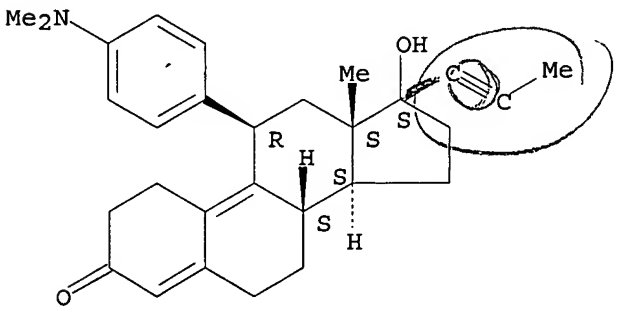
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

34 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
34 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> dimethylamino

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 84371-65-3 REGISTRY
CN Estra-4,9-dien-3-one, 11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-, (11.beta.,17.beta.)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 17.beta.-Hydroxy-11.beta.-[4-(dimethylamino)-phenyl]-17.alpha.-(prop-1-ynyl)-estra-4,9-dien-3-one
CN CDB 2477
CN Mifegyne
CN Mifeprex
CN Mifepristone
CN Mifestone
CN R 38486
CN RU 38486
CN **RU 486**
CN RU 486-6
CN RU486
FS STEREOSEARCH
DR 122742-25-0, 83203-42-3
MF C29 H35 N O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, HSDB*, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



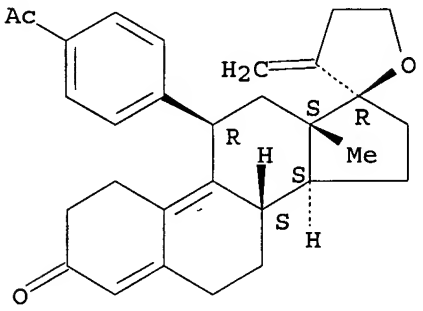
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1869 REFERENCES IN FILE CA (1907 TO DATE)
59 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1872 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 155768-17-5 REGISTRY
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-(4-acetylphenyl)-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[17H-cyclopenta[a]phenanthrene-17,2'(3'H)-furan], 19,24-dinorchola-4,9,20-trien-3-one deriv.
OTHER NAMES:
CN **Org 33628**
FS STEREOSEARCH
MF C30 H34 O3
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, DRUGNL, DRUGUPDATES, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES IN FILE CAPLUS (1907 TO DATE)

ANSWER 1 OF 19 CAPLUS COPYRIGHT 2003 ACS

AN 1999:180237 CAPLUS

DN 131:773

TI Mechanism of action and clinical effects of antiprogestins on the non-pregnant uterus

AU Spitz, Irving M.; Robbins, Ann

CS Shaare Zedek Medical Center, Institute of Hormone Research, Jerusalem, 91031, Israel

SO Human Reproduction Update (**1998**), 4(5), 584-593
CODEN: HRUPF8; ISSN: 1355-4786

PB Oxford University Press

DT Journal; General Review

LA English

AB A review, with 71 refs. Considerable progress has been made in elucidating the mechanism of action of **antiprogestins**. The biol. response to a progesterone antagonist depends on many factors. The usual effect is that of an antagonist, but progesterone agnostic or even anti-estrogenic or estrogenic effects have also been obsd. The present review focuses on the clin. applications of **antiprogestins** in the non-pregnant uterus. Whereas high doses of **antiprogestins** block ovulation, low doses impair endometrial development without affecting ovulation, hormonal levels or **bleeding** patterns. Indeed, the endometrium is the tissue which is the most sensitive to **antiprogestins**. The effect of **antiprogestins** is to produce a delay in endometrial maturation and to postpone the appearance of the implantation window. This concept of 'endometrial contraception' requires further testing in humans, although the principle has been proven in monkeys. In contrast to the low doses of mifepristone which delay endometrial maturation, a min. dose of 50 mg is required to produce endometrial **bleeding**. Late luteal phase **antiprogestin** administration does not disturb ovulation, hormonal levels or **bleeding** patterns. This has clin. application, and mifepristone has been used together with prostaglandins in women with delayed **menses** to successfully prevent implantation. Mifepristone has also been shown to be an effective post-coital agent. However, when used on a regular basis once monthly at the end of the cycle as a potential contraceptive, the results are disappointing. Because of their antiproliferative and anti-estrogenic effects on the endometrium, **antiprogestins** are also used in the treatment of estrogen-dependent conditions such as endometriosis and fibromyomas. In humans, chronic administration of high doses of **antiprogestins** has on rare occasions been assocd. with endometrial hyperplasia, presumably a consequence of unopposed estrogen activity. This does not occur with low doses (1 mg daily for 5 mo).

RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2003 ACS

AN 1998:369363 CAPLUS

DN 129:117956

TI Effects of long-term low-dose mifepristone on reproductive function in women

AU Croxatto, H. B.; Kovacs, L.; Massai, R.; Resch, B. A.; Fuentealba, B.; Salvatierra, A. M.; Croxatto, H. D.; Zalanyi, S.; Viski, S.; Krenacs, L.

CS Instituto Chileno de Medicina Reproductive (ICMER), Santiago, Chile

SO Human Reproduction (**1998**), 13(4), 793-798
CODEN: HUREEE; ISSN: 0268-1161

PB Oxford University Press

DT Journal

LA English

AB Low-dose **antiprogestin** administration has been proposed as a new contraceptive modality to interference with endometrial receptivity without disturbing ovarian function. The effects of 1 mg/day mifepristone for 150 days on the **menstrual** cycle were assessed in 21

surgically sterilized women. The aim was to study each woman for one control cycle and during months 1, 3 and 5 of treatment. Ovulation, endometrial thickness, serum estradiol and progesterone, urinary LH, endometrial morphol. and cervical mucus were assessed. Luteal phase progesterone concns. were obsd. in 36 of the 60 treated months assessed and less frequently as treatment progressed. The **bleeding** pattern was regular in most biphasic cycles, while prolonged interbleeding intervals or no **bleeding** were assocd. with monophasic cycles. Altered endometrial morphol. was found in all cases irresp. of the occurrence of luteal activity. Increased endometrial thickness and dilated glands were obsd. in 25 and 34% resp. of the monophasic cycles. Mifepristone, 1 mg/day, interferes with endometrial development while allowing the occurrence of biphasic ovarian cycles and regular **bleeding**. However, it also prevents ovarian cyclicity in a high proportion of treated months, and this is assocd. with increased endometrial growth in some women, which may be of concern.

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1997:698721 CAPLUS
DN 127:326621
TI Antiprogestin action on the endometrium
AU Nieman, Lynnette
CS Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, 20892, USA
SO Annals of the New York Academy of Sciences (**1997**), 828(Uterus: Endometrium and Myometrium), 103-107
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal; General Review
LA English
AB A review, with 28 refs. discussing the endometrial effects of the best-studied **antiprogestin**, RU 486, in women and other primates. Emphasis is placed on morphol. and functional changes in the endometrium, as well as the ability to interrupt pregnancy or induce **menstrual bleeding**.

L5 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1997:306221 CAPLUS
DN 126:338999
TI Early luteal phase administration of mifepristone inhibits preimplantation embryo development and viability in the rhesus monkey
AU Ghosh, Debabrata; Kumar, P. G. Luther Lalit; Sengupta, Jayasree
CS Department of Physiology, All India Institute of Medical Sciences, New Delhi, 110 029, India
SO Human Reproduction (**1997**), 12(3), 575-582
CODEN: HUREEE; ISSN: 0268-1161
PB Oxford University Press
DT Journal
LA English
AB It is generally believed that progesterone is essential for inducing the changes in oviduct and uterus necessary for embryo viability and implantation in a no. of mammalian species. The aim of this study was, in the rhesus monkey, to examine in conception cycles with and without early luteal phase **antiprogestin** (mifepristone; RU 486) treatment: (i) the growth status of preimplantation embryos and (ii) the implantation ability of the pre-implantation embryo after transfer to a synchronous-cycle surrogate recipient. A total of 43 proven fertile rhesus monkeys were randomly placed in the control (group 1) and mifepristone (group 2) groups. All monkeys cohabited with proven fertile male monkeys on cycle days 8-16 and were injected with vehicle alone [benzyl benzoate:olive oil, 1:4 (vol./vol.), s.c.] for group 1 and with mifepristone (2 mg/kg body wt. s.c.) for group 2, on day 2 after the

presumed day of ovulation. A total of 12 preimplantation embryos [premorula, morula, zona-encased and zona-free blastocysts and degenerate embryos] were recovered from 17 ovulatory, mated cycles in group 1 on day 6 after ovulation. In group 2, of the 23 ovulated cycles, 12 preimplantation embryos [premorula, morula, zona-encased blastocyst, and degenerate embryos] were retrieved. Despite no significant difference in the recovery rate between the two groups, early luteal phase RU 486 exposure induced delay in preimplantation embryo growth, primarily at the morula-blastocyst transition stage. Nine of the embryos from group 1 and seven of the embryos from group 2 recovered on day 6 were transferred to naturally synchronized, non-mated and untreated surrogate recipients. In group 1, five embryos implanted (55%) and, of these, three (60%) gave rise to live infants through natural delivery; implantation was assessed from extension of the cycle (i.e. no **menstrual bleeding**)
and rise in concns. of estradiol and progesterone from day 10 of conception; rectal palpation was performed on cycle day 50 to confirm clin. pregnancy. In group 2, however, there was not a single case of establishment of pregnancy following transfer of embryos retrieved from mifepristone-exposed monkeys. Thus, preimplantation embryos recovered from RU 486-exposed monkeys failed to establish evolutive implantation and pregnancy, while significant success was obsd. in transfers of embryos from the control group. The authors postulate that progesterone-mediated actions are involved in mediating the growth and viability of preimplantation-stage embryos in the rhesus monkey.

L5 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1997:173267 CAPLUS
DN 126:220799
TI Effect of low daily doses of mifepristone on ovarian function and endometrial development
AU Danielsson, K. Gemzell; Swahn, M. -L.; Westlund, P.; Johannisson, E.; Seppala, M.; Bygdeman, M.
CS Division for Obstetrics and Gynecology, Karolinska Hospital, Stockholm, Swed.
SO Human Reproduction (**1997**), 12(1), 124-131
CODEN: HUREEE; ISSN: 0268-1161
PB Oxford University Press
DT Journal
LA English
AB The effects of low daily doses of the **antiprogestin** mifepristone (RU 486) on ovarian and endometrial function were studied. The study included one control cycle, three treatment cycles and one follow-up cycle. During the treatment cycles, either 0.1 or 0.5 mg of mifepristone was administered once daily. Urine samples were collected three times weekly during the control and treatment cycles and pregnanediol glucuronide and estrone glucuronide and LH were quantified by radio-immunoassay. Blood samples for cortisol measurement were collected once weekly and for serum glycodelin at the onset of menstruation. An endometrial biopsy was obtained in the mid-luteal phase in the control cycle and in the first and third treatment cycles and analyzed by morphometric and histochem. methods. Binding of Dolichus biflorus agglutinin (DBA) lectin was measured and expression of progesterone and estrogen receptors and glycodelin were analyzed immunohistochem. All cycles studied were ovulatory with an LH peak nd elevated pregnanediol glucuronide concns. Follicular development seemed normal as judged by ultrasound examn. The length of the **menstrual** cycle and the **menstrual bleeding** were not significantly altered.
Following administration of 0.5 mg mifepristone/day, endometrial development appeared to be slightly retarded and glandular diam. was significantly reduced. Furthermore, significant decreases in DBA lectin binding and endometrial expression of glycodelin were obsd. Daily doses of 0.1 mg did not have any significant effect on the endometrium. No differences in estrogen or progesterone receptor immunoactivity between control and treatment cycles were seen. This study provides further

evidence that endometrial function is sensitive even to doses of **antiprogestin** that are low enough not to disturb ovulation. It remains to be established whether these effects are sufficient to prevent implantation.

L5 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1995:940328 CAPLUS
DN 123:330242
TI Onapristone (ZK 98.299): A potential antiprogestin for endometrial contraception
AU Katkam, Rajendra R.; Gopalkrishnan, Kamla; Chwalisz, Kristof; Schillinger, Eckard; Puri, Chander P.
CS Institute Research Reproduction, Bombay, 400012, India
SO American Journal of Obstetrics and Gynecology (**1995**), 173(3, Pt. 1), 779-87
CODEN: AJOGAH; ISSN: 0002-9378
PB Mosby-Year Book
DT Journal
LA English
AB The effects of the **antiprogestin** onapristone (ZK 98.299) on fertility; **menstrual** cycle length; duration of **menses**; serum estradiol, progesterone, and cortisol concns.; and endometrial morphol. features were studied in adult bonnet monkeys. Five animals were treated s.c. with the vehicle and another nine with either 2.5 or 5 mg of onapristone per animal. Treatment was initiated on day 5 of the first treatment cycle, and thereafter onapristone was administered every third day for four to seven consecutive cycles. The females were placed with adult males during the periovulatory period, which was assessed by frequent anal. of serum estradiol concns. In the final treatment cycle an endometrial biopsy was performed on day 8 after a midcycle estradiol peak in the ovulatory cycle, or around day 20 if the cycle was anovulatory. Blood samples for estradiol, progesterone, and cortisol measurement were collected every third day, except for the periovulatory period when sampling was more frequent. Each of the five animals treated with the vehicle became pregnant: one in the first, three in the second, and one in the third mated cycle, whereas only one of nine treated with onapristone became pregnant. Four animals treated with 2.5 mg of onapristone for 17 cycles and another four treated with a 5 mg dose for 21 cycles did not conceive. In eight animals that did not conceive the first three treatment cycles of six were ovulatory, and in the remaining two animals two cycles of each were ovulatory. During treatment the mean **menstrual** cycle length was not altered significantly; however, in one it was shortened and in another two it was prolonged. Similarly, the mean duration of **menses** was not significantly affected, but in some cycles it was reduced. Moreover, there was only slight **bleeding** in some treatment cycles. Ovulation occurred in 30 of 45 treatment cycles, including the final treatment cycle during which the biopsy was taken, as indicated by serum estradiol and progesterone concns. In some of the ovulatory cycles prolonged treatment suppressed luteal activity; however, in the ovulatory cycles the duration of follicular and luteal phases was not significantly affected. In the anovulatory cycles there was a delayed increase in serum estradiol concns., suggesting a partial inhibition of folliculogenesis. In treated animals endometrial growth and development was retarded and rendered out of phase. In animals treated with the higher (5 mg) onapristone dose the endometrial glands had partially regressed, the secretory activity was blocked, and stromal compaction was evident. The treatment had no significant effect on serum cortisol levels. This study demonstrates that low-dose onapristone treatment throughout the **menstrual** cycle prevents pregnancy without disturbing the **menstrual** cycle and ovulation in the majority of cycles. However, anovulation and luteal insufficiency occurred in some animals during prolonged treatment. The contraceptive effect in the ovulatory cycles seems primarily related to the retardation of endometrial development resulting in the inhibition of endometrial

receptivity. It appears likely that a dose or treatment regimen of onapristone that will inhibit endometrial receptivity and prevent implantation without affecting the **menstrual** cycle even on prolonged treatment could be identified.

L5 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1995:533948 CAPLUS
DN 122:282470
TI Effects of intermittent antiprogestin RU486 combined with cyclic medroxyprogesterone acetate on folliculogenesis and ovulation
AU Kekkonen, Raimo; Croxatto, Horacio B.; Lahteenmaki, Pekka; Salvatierra, Ana Maria; Tuominen, Juhani
CS Department Medical Chemistry, University Helsinki, Helsinki, SF-00014, Finland
SO Human Reproduction (**1995**), 10(2), 287-92
CODEN: HUREEE; ISSN: 0268-1161
DT Journal
LA English
AB The results of several studies have suggested an inhibitory effect of the **antiprogestin** RU486 on late stages of folliculogenesis and ovulation. To assess the feasibility of using this property to inhibit ovulation without losing cycle control, an intermittent administration of RU486 alternated with medroxyprogesterone acetate (MPA) was tested in a phase I study. RU486 at a dose of 50 mg/day was given on **menstrual** cycle days 9-11 and 27-29, and 10 mg/day of MPA was given on cycle days 17-26 for three consecutive cycles to six Finnish and five Chilean women. Blood samples were collected two to three times a week for serum progesterone and estradiol assays in three treatment cycles. One control cycle and one post-treatment recovery cycle were also monitored by serum samplings. Ultrasonog. was carried out to measure follicular diams. in the treatment cycles. In 29 of 32 cycles, **bleeding** commenced within 3 days after the last MPA pill intake. Out of 32 treatment cycles, 20 were without luteal activity (serum progesterone <9 nmol/L). Although 12 treatment cycles showed luteal activity (serum progesterone .gtoreq.9 nmol/L), a clear rupture of a pre-ovulatory follicle >15 mm, verified by ultrasonog., was seen in only one treatment cycle. During the treatment cycles with luteal activity (serum progesterone levels .gtoreq.9 nmol/L), serum estradiol concns. were significantly higher on cycle days 9-18 and significantly lower at the end of the cycle compared with the cycles without luteal activity. The regimen used in this study disturbed folliculogenesis and ovulation (apparently), and was able to provide good cycle control in the majority of the cycles.

L5 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1994:96097 CAPLUS
DN 120:96097
TI Treatment with a progesterone antagonist ZK 98.299 delays endometrial development without blocking ovulation in bonnet monkeys
AU Ishwad, P.C.; Katkam, R.R.; Hinduja, I.N.; Chwalisz, K.; Elger, W.; Puri, C.P.
CS Inst. Res. Reprod., Bombay, 400012, India
SO Contraception (**1993**), 48(1), 57-70
CODEN: CCPTAY; ISSN: 0010-7824
DT Journal
LA English
AB The effects of an **antiprogestin** ZK 98.299 (onapristone) on serum levels of estradiol and progesterone, and on the endometrial morphol. were studied in adult bonnet monkeys. Twelve animals having **menstrual** cycles of normal duration (24 to 30 days) were randomly distributed into 4 equal groups. The animals in Group 1 were treated (s.c.) with the vehicle (benzyl benzoate: castor oil, 1:10), and in Groups 2, 3 and 4 with 5 mg, 10 mg, or 20 mg ZK 98.299 once-a-week, resp. Treatment was initiated on day 1 of the **menstrual** cycle and each animal in Groups 1, 2 and

3 was treated for two consecutive cycles. Since the treatment cycle length of animals in Group 4 was considerably prolonged, they were treated for one **menstrual** cycle only. Endometrial biopsy was taken around day 20 of the second treatment cycle of first three groups and around day 50 of the 4th group of animals. Treatment with vehicle or 5 mg ZK 98.299 had no significant effect on the **menstrual** cycle length. Treatment with 10 mg dose had no effect in two animals and prolonged the cycle length in one, whereas, further increase in the dose to 20 mg prolonged the cycle length in all the animals. The duration of **menses** was generally reduced. Treatment with vehicle or different doses of ZK 98.299 had no effect on ovulation. In animals treated with 5 or 10 mg dose, the pattern of mid cycle rise in serum estradiol levels and progesterone levels during the luteal phase of both treatment cycles were comparable to those of vehicle-treated animals and were suggestive of normal ovulatory cycles. In animals treated with the higher dose (20 mg/wk), progesterone levels during the luteal phase were significantly reduced and were indicative of luteal insufficiency. The hormonal data during the treatment period of this group of animals was suggestive of two distinct ovarian cycles indicating that the **menstrual bleeding** during the treatment period was probably very scanty. Treatment with ZK 98.299 impaired the endometrial development in a dose-dependent manner. In vehicle-treated animals, the endometrium had large and tortuous glands with secretions. Treatment with ZK 98.299 caused atrophic changes in the glands as well as in the stroma. The height of the epithelial cells was markedly decreased and they became small and inactive. This study, therefore, suggests that treatment with low doses of **antiprogestin** ZK 98.299 at weekly intervals does not block folliculogenesis or ovulation, but has an inhibitory effect on the endometrium. This study opens up a possibility of development of **antiprogestins** as a contraceptive agent.

L5 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1994:24365 CAPLUS
DN 120:24365
TI Anti-progestin for minimizing progestin-associated breakthrough bleeding
IN Hodgen, Gary D.
PA Medical College of Hampton Roads, USA
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9321926	A1	19931111	WO 1992-US3574	19920506	<--
	W: AU, CA, JP, KR, US					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE					
	AU 9219180	A1	19931129	AU 1992-19180	19920506	<--
	WO 9321927	A1	19931111	WO 1993-US4003	19930503	<--
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	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	AU 9343685	A1	19931129	AU 1993-43685	19930503	<--
	AU 667729	B2	19960404			
	EP 646008	A1	19950405	EP 1993-913781	19930503	<--
	EP 646008	B1	19991215			
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	ES 2142345	T3	20000416	ES 1993-913781	19930503	
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	CN 1079651	A	19931222	CN 1993-105281	19930506	<--
	CN 1073422	B	20011024			
	FI 9405207	A	19941104	FI 1994-5207	19941104	<--
	NO 9404210	A	19941104	NO 1994-4210	19941104	<--

PRAI WO 1992-US3574 A 19920506
WO 1993-US4003 A 19930503

AB A method is disclosed for minimizing **menstrual bleeding** irregularities in individuals using progestin-only pharmaceutical prepns., e.g. contraceptives. The method involves administration of a biol. effective amt. of an **anti-progestin**. The **bleeding**-control effect of RU 486 was demonstrated in primates receiving levonorgestrel and RU 486.

L5 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1993:642066 CAPLUS
DN 119:242066
TI Estrogen/progestin/antiprogestin method and kit for oral contraception and regulating menses
IN Hodgen, Gary D.; Chwalisz, Krzysztof
PA Schering A.-G., Germany
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9317686	A1	19930916	WO 1993-US1931	19930302	<--
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	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG					
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	AU 678150	B2	19970522			
	CN 1079386	A	19931215	CN 1993-102182	19930302	<--
	CN 1090481	B	20020911			
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	EP 630246	A1	19941228	EP 1993-907185	19930302	<--
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	JP 07509218	T2	19951012	JP 1993-515869	19930302	<--
	PL 172790	B1	19971128	PL 1993-316357	19930302	<--
	BR 9306005	A	19980623	BR 1993-6005	19930302	<--
	IL 104915	A1	19980715	IL 1993-104915	19930302	<--
	PL 174785	B1	19980930	PL 1993-304807	19930302	<--
	RU 2127112	C1	19990310	RU 1994-40720	19930302	
	FI 9404022	A	19940901	FI 1994-4022	19940901	<--
	NO 9403234	A	19941101	NO 1994-3234	19940901	<--
	CN 1395932	A	20030212	CN 2002-101583	20020110	
PRAI	US 1992-843058	A2	19920302			
	WO 1993-US1931	A	19930302			

AB **Menses** regulation and, when desired, contraception are achieved at low doses of estrogen and progestin, which otherwise would create episodes of breakthrough **bleeding** and/or withdrawal amenorrhea, by periodically inducing **menses** with an **antiprogestin**. In studies with primates receiving ultra-low doses of contraceptive (norethindrone acetate-ethinyl estradiol), intermittent administration of RU 486 (Mifepristone) reduced breakthrough **bleeding** in the intermenstrual intervals; reliable **menstrual** induction at the expected time was also obsd., thus eliminating withdrawal amennorhea. A study to evaluate breakthrough **bleeding** prior to and after onapristone treatment in ovariectomized monkeys receiving estrogen and estrogen plus progesterone replacement therapy is also described.

L5 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1993:531796 CAPLUS
DN 119:131796
TI Early luteal phase treatment with mifepristone (RU 486) for fertility regulation

AU Gemzell-Danielsson, K.; Swahn, M. L.; Svalander, P.; Bygdeman, M.
CS Dep. Obstet. Gynaecol., Karolinska Hosp., Stockholm, S-104 01, Swed.
SO Human Reproduction (**1993**), 8(6), 870-3
CODEN: HUREEE; ISSN: 0268-1161
DT Journal
LA English
AB Mifepristone (RU 486) is an **antiprogestin** which interacts with progesterone at the receptor level. Administration of mifepristone immediately after ovulation does not upset the **menstrual** cycle. However, the maturation and function of the endometrium is inhibited and uterine contractility is changed. To test if these effects are sufficient to prevent implantation, 21 women agreed to use one single treatment with 200 mg mifepristone on day LH + 2 monthly as their only contraceptive method. The women were treated for 1-12 mo. The time of the LH peak was detd. in the urine by the women themselves using a rapid LH test (Ouv-quick, Organon). The overall no. of cycles studies was 169. In 12 cycles the women were unable to detect the LH peak. In these cycles no treatment was given and the women were advised to use barrier methods during the time to menstruation. The remaining 157 cycles with a detectable LH peak were all ovulatory based on plasma progesterone measurement. One pregnancy occurred. On the basis of the time of the LH peak, it was retrospectively calcd. that in 124 cycles at least one act of intercourse occurred during the period 3 days before to 1 day after ovulation. The probability of pregnancy in this period of the **menstrual** cycle is thus 0.008. The women did not complain of any treatment-related side-effects apart from slight **bleeding** for 2-3 days starting a few days after the day of treatment in 35% of the cycles. The results show that the effect of mifepristone on the endometrium is sufficient to prevent pregnancy and indicate that treatment with **antiprogestin** can also be used for contraceptive purposes.

L5 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1987:509603 CAPLUS
DN 107:109603
TI Induction of menstruation by antiprogesterone ZK 98.299 in cycling bonnet monkeys
AU Puri, C. P.; Elger, W. G.; Pongubala, J. M. R.
CS Inst. Res. Reprod., Bombay, 400 012, India
SO Contraception (**1987**), 35(4), 409-21
CODEN: CCPTAY; ISSN: 0010-7824
DT Journal
LA English
AB The **antiprogestin** ZK 98.299 (I) was administered s.c. (30 mg/day) to 2 groups of cycling bonnet monkeys. In group I, I was injected from day 16 to 18 and in Group II from day 21 to 23 of the cycle. Each animal served as its own control and in the pretreatment cycle the vehicle (benzyl benzoate: castor oil, 1:4) was administered. During the treatment cycle of these animals, the peak in estradiol levels was obsd. between days 8 to 11 of the **menstrual** cycle. In Group I animals, administration of I induced vaginal **bleeding** in 3 of the 6 animals in <2 days of its 1st injection. In the remaining 3 animals, the **menstrual** cycle length was prolonged. However, in all 6 animals a premature drop in serum progesterone levels was obsd. On the other hand, in Group II in 7 animals with ovulatory treatment cycles, administration of I induced vaginal **bleeding** in <4 days of the 1st dose and significantly shortened the cycle length. A significant decline in progesterone levels was obsd. in these animals also. However, in 2 animals in each group, I induced vaginal **bleeding** while the serum progesterone levels were still high. Posttreatment cycles were ovulatory but the cycle length was marginally increased in some animals. In 2 animals of Group II, in which the treatment cycle turned out to be anovulatory, I did not induce **bleeding** and had no effect on serum progesterone levels. When administered during the luteal phase, I induces vaginal **bleeding** and premature luteal regression in

bonnet monkeys. However, induction of vaginal **bleeding** may not be assocd. with drop in progesterone levels. I, therefore, appears to have potential for fertility control which warrants clin. evaluation.

L5 ANSWER 13 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1998232890 EMBASE
TI [The endometrial approach of contraception].
APPROCHE ENDOMETRIALE DE LA CONTRACEPTION.
AU Levy D.; Christin-Maitre S.; Chabbert-Buffet N.; Bergeron C.; Coeling-Bennink H.J.C.D.; Freitas S.; Pintiaux A.; Bouchard I.P.
CS D. Levy, Service d'Endocrinologie, Hopital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75012 Paris, France
SO References en Gynecologie Obstetrique, (**1997**) 5/3 (249-262).
Refs: 108
ISSN: 1244-8168 CODEN: RGOBE2
CY France
DT Journal; General Review
FS 003 Endocrinology
010 Obstetrics and Gynecology
037 Drug Literature Index
LA French
SL English; French
AB A contraceptive method that would interfere only with uterine receptivity, thereby respecting the endocrine events of the ovarian cycle is a key issue in reproductive medicine. This type of endometrial contraception would be interesting for women presenting cardiovascular risk factors and thus at risk for thrombotic incidents. It could also be a good contraceptive alternative for women wishing an efficient, convenient, safe and well tolerated contraceptive method. The present work reviews the current knowledge of the molecular and cellular events of endometrial physiology during the **menstrual** cycles as well as the mechanisms of action of hormonal contraception. We then describe our understanding of the mechanisms of endometrial **bleeding** and the role of molecules such as matrix metalloproteinases and vascular endothelial growth factor (VEGF) in **menstrual** and intermenstrual **bleeding**.
Finally, possible molecular and cellular targets specific to the endometrium are defined, particularly progesterone and its receptor, endometrial integrins expressed during the implantation window in human endometrium and insuline growth factor binding protein (IGFBP-1). A special interest is devoted to the **antiprogestin** agents such as mifepristone and to intrauterine administration of steroids, the use of which still needs to be defined for a an effective and well tolerated contraceptive action.

L5 ANSWER 14 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 97015912 EMBASE
DN 1997015912
TI Biological mechanisms underlying the clinical effects of RU 486: Modulation of cultured endometrial stromal cell stromelysin-1 and prolactin expression.
AU Schatz F.; Papp C.; Aigner S.; Krikun G.; Hausknecht V.; Lockwood C.J.
CS F. Schatz, Department of Obstetrics/Gynecology, New York University Medical Center, 550 First Avenue, New York, NY 10016, United States
SO Journal of Clinical Endocrinology and Metabolism, (**1997**) 82/1 (188-193).
Refs: 40
ISSN: 0021-972X CODEN: JCEMAZ
CY United States
DT Journal; Article
FS 003 Endocrinology
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English

AB During in vitro decidualization of human endometrial stromal cells (HESCs), medroxyprogesterone acetate (MPA) inhibits expression of the potent extracellular matrix (ECM)-degrading protease stromelysin-1 (MMP-3), but enhances PRL expression. Consistent with its priming role in vivo, estradiol (E2) augments these effects. In the current study, immunoblot analysis revealed that coincubation with 10-6 M RU 486 blocked the inhibition in HESC-secreted MMP-3 levels (50,000 mol wt) evoked by 10-8 M E2 + 10-7 M MPA. Although MPA can act as a glucocorticoid, the HESCs were refractory to 10-7 M dexamethasone added alone or with E2. Because E2 elevates progesterone but not glucocorticoid receptor levels, MPA and RU 486 control MMP-3 expression as a progestin and **antiprogestin**, respectively. To study RU 486 involvement in steroid withdrawal leading to menstruation, HESCs were decidualized during 10 days incubation with E2 + MPA, and parallel cultures were kept in E2 + MPA or withdrawn to either control or RU 486-containing medium. Compared with E2 + MPA-suppressed HESCs, increases in levels of secreted MMP-3 (2.0-fold), and its 2.1-kilobase messenger RNA (10-fold) were observed in HESCs after 4 days of withdrawal to control medium, with much greater increases seen in RU 486-containing medium (10-fold protein, 100- fold messenger RNA). Previously, we showed that RU 486 up-regulated E2 + MPA-inhibited plasminogen activator expression in the cultured HESCs. Extrapolation of these in vitro observations to endometrial events following RU 486 administration suggests that coordinate enhancement of MMP-3 and plasminogen activator expression promotes proteolysis of the stromal/decidual ECM, which leads to endometrial sloughing. Moreover, destabilization of endometrial microvessels resulting from degradation of their surrounding ECM is consistent with the heavy **menstrual bleeding** stemming from RU 486 administration. However, in contrast to the marked RU 486-initiated reversal of MMP-3 expression, RU 486 did not significantly reverse E2 + MPA-enhanced PRL secretion by the cultured HESCs. Interestingly, decidual PRL, unlike decidual MMP-3, does not appear to play a role in menstruation. Interleukin- 1.beta. counteracted E2 + MPA-mediated inhibition of secreted MMP-3 levels, implying that leukocyte/trophoblast-derived cytokines can modulate steroid- regulated MMP-3 expression by stromal/decidual cells during menstruation and pregnancy.

L5 ANSWER 15 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 93354705 EMBASE
DN 1993354705
TI Clinical applications of the antiprogestin RU 486.
AU Spitz I.M.; Bardin C.W.
CS Population Council, 1230 York Avenue,New York, NY 10021, United States
SO Endocrinologist, (**1993**) 3/1 (58-66).
ISSN: 1051-2144 CODEN: EDOCEB
CY United States
DT Journal; General Review
FS 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Administration of the **antiprogestin** RU 486 to pregnant women with amenorrhea of 7 weeks or less induced abortion in 65 to 85% of subjects. The addition of prostaglandins increases the efficacy to 95%. Excessive uterine **bleeding** necessitates vacuum aspiration or dilation and curettage in 0.9% of subjects. Although follicular phase RU 486 administration postpones the LH surge and delays ovulation, intermittent once-weekly administration did not consistently block ovulation. When RU 486 was used in unprotected women as a monthly **menses** regulator, some pregnancies still continued. As a postcoital agent, RU 486 is as effective as other currently available methods. Since RU 486 dilates and softens the cervix, it may have a role

in prostaglandin- induced second trimester abortion. It also promotes labor following intrauterine fetal death. RU 486 might also be useful to induce spontaneous labor at term. Since RU 486 has both agonistic and antagonistic actions on the endometrium and breast, there have been preliminary studies on its use in treatment of endometriosis and breast carcinoma, as well as in inoperable meningiomas. RU 486 has also ameliorated clinical and biochemical manifestations of Cushing's syndrome consequent to ACTH-producing tumors and adrenal carcinoma.

L5 ANSWER 16 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 93250780 EMBASE
DN 1993250780
TI Termination of pregnancy with reduced doses of mifepristone.
AU Van Look P.F.A.; Henshaw R.; Norman J.; Thong K.J.; Gomez Alzugaray M.; Ho P.C.; Pretnar-Darovec A.; Sajina B.; Perotti L.; Wyssling H.; Chen J.-K.; Zhu J.-H.; Swahn M.L.; Kovacs L.; Guocsai G.; Song L.; Wang Y.-J.; Belsey E.M.; Berners-Lee N.; et al.
CS Special Programme of Research, Devel./Res. Training Human Reprod., World Health Organization, Avenue Appia,1211 Geneva 27, Switzerland
SO British Medical Journal, (**1993**) 307/6903 (532-537).
ISSN: 0959-8146 CODEN: BMJOAE
CY United Kingdom
DT Journal; Article
FS 003 Endocrinology
010 Obstetrics and Gynecology
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Objectives - To compare the abortifacient efficacy and side effects of three doses of the **antiprogestin** mifepristone plus prostaglandin for termination of early pregnancy. Design - Randomised, double blind multicentre trial. Setting - 11 departments of obstetrics and gynaecology and of family planning, mostly in university hospitals, in seven countries. Subjects - 1182 women with an early pregnancy (**menstrual** delay of 7-28 days) requesting abortion. Interventions - Single doses of 200 mg, 400 mg, or 600 mg mifepristone followed, 48 hours later, by vaginal pessary of 1 mg of the prostaglandin E1 analogue gemeprost. Main outcome measures - Outcome of treatment; duration and subjective amount of **menstrual bleeding**; side effects and complications; and concentration of haemoglobin. Results - Outcome was similar with the three doses of mifepristone. Of the 1151 women with known outcome, 95.5% had a complete abortion (364 (93.8%) of those given 200 mg mifepristone, 368 (94.1%) of those given 400 mg, and 367 (94.3%) of those given 600 mg), 3.7% had an incomplete abortion (14 (3.6%), 15 (3.8%), and 14 (3.6%)), 0.3% had a missed abortion (three (0.8%), one (0.3%), and none), and 0.4% had a continuing live pregnancy (two (0.5%), two (0.5%), and one (0.3%)). Of the 43 women who had incomplete abortion, 23 underwent emergency uterine curettage (usually for haemostatic purposes) and three of these women who had incomplete abortion, 23 underwent emergency uterine curettage (usually for haemostatic purposes) and three of these women were given a blood transfusion. The numbers of reported complaints, **bleeding** patterns, and changes in blood pressure and haemoglobin concentrations were similar with the three treatments. Conclusions - For termination of early pregnancy a single dose of 200 mg mifepristone is as effective as the currently recommended dose of 600 mg when used in combination with a vaginal pessary of 1 mg gemeprost.

L5 ANSWER 17 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 90074747 EMBASE
DN 1990074747
TI Contragestion with RU 486: A new approach to postovulatory fertility

control.
AU Baulieu E.-E.
CS INSERM U33, Faculte de Medecine Paris-Sud, Laboratoire d'Hormones,94275 Bicetre Cedex, France
SO Acta Obstetricia et Gynecologica Scandinavica, Supplement, (**1989**) -/149 (5-8).
ISSN: 0300-8835 CODEN: AGSSAI
CY Sweden
DT Journal; Conference Article
FS 010 Obstetrics and Gynecology
037 Drug Literature Index
LA English
SL English
AB The steroidal derivative RU 486 (17.beta.-hydroxy-11.beta.-(4-dimethyl-aminophenyl)-17.alpha.-(prop-1-ynyl) estra-4,9-dien-3-one) is the first potent **antiprogestin** to be used clinically. RU 486 blocks the action of progesterone by a reversible inhibition of the action of progesterone on its own receptors. This reversibility allows endocrine functions to return quickly to normal after discontinuation of treatment. However, target cells which depend upon a continuity of progesterone action will be irreversibly disrupted by receptor blockade. In normal women, RU 486 acts during the luteal phase in the endometrium, provoking **bleeding**, and decreasing pituitary luteinizing hormone (LH) secretion and hence luteolysis. In pregnant women, it affects the decidua, increases myometrial contractility and ripening of the cervix and ultimately leads to termination of pregnancy. Detachment of the trophoblast leads to a further fall in gonadotropin production. Clinical studies indicate that RU 486 can be a very efficient agent for the termination of early pregnancy, and as a postcoital **menstrual** regulator. In about 20% of cases when RU 486 is given alone, termination of pregnancy fails. This can be overcome by taking in addition a small amount of prostaglandin.

L5 ANSWER 18 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 90069070 EMBASE
DN 1990069070
TI Termination of early pregnancy with RU 486 (mifepristone) in combination with a prostaglandin analogue (sulprostone).
AU Swahn M.-L.; Bygdeman M.
CS Department of Obstetrics and Gynecology, Karolinska Sjukhuset, Stockholm, Sweden
SO Acta Obstetricia et Gynecologica Scandinavica, (**1989**) 68/4 (293-300).
ISSN: 0001-6349 CODEN: AOGSAE
CY Sweden
DT Journal; Article
FS 010 Obstetrics and Gynecology
037 Drug Literature Index
LA English
SL English
AB The **antiprogestin** RU 486 (mifepristone) has been shown to induce abortion when administered in early pregnancy, but the rate of incomplete abortion is high, around 40%. As blockage of the progesterone receptor increases the myometrial sensitivity to prostaglandins, a combination of RU 486 and a prostaglandin E2-analogue was tested for termination of pregnancy. One hundred and sixteen women, with a gestational length of less than 49 days from the first day of the last **menstrual** period, were treated with a daily dose of 50 or 100 mg RU 486 for 3 to 6 days, complemented with an intramuscular dose of 0.25 mg sulprostone (16-phenoxy-PGE2-sulfonylamide) on the last day of RU 486 treatment. The results confirmed that a reduction of treatment duration to 3 days is just as effective for inducing abortion (91% complete abortion) as a 4-6-day treatment regimen (95% complete abortion). Six patients had an incomplete abortion and in one the pregnancy continued unaffected. Side effects

included intense uterine pain after the prostaglandin administration (16%), vomiting associated with the **antiprogestin** intake (9%) and after the prostaglandin administration (9%). One woman needed emergency curettage due to heavy **bleeding**. six percent of the treated patients had a decrease in hemoglobin exceeding 20 g/l during the first week but no patient needed blood transfusion. No serious side effects were recorded.

L5 ANSWER 19 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 88042755 EMBASE
DN 1988042755
TI Contragestion by antiprogestin RU 486: A review.
AU Baulieu E.E.; Ulmann A.; Philibert D.
CS Universite Paris-Sud, Lab-Hormones, INSERM U 33, 94275 Bicetre, France
SO Archives of Gynecology and Obstetrics, (**1987**) 241/2 (73-85).
ISSN: 0932-0067 CODEN: AGOBEJ
CY Germany
DT Journal
FS 003 Endocrinology
010 Obstetrics and Gynecology
037 Drug Literature Index
LA English
SL English
AB The steroidal derivative RU 486 (17.beta.-hydroxy-11.beta.-(4-dimethylaminophenyl)-17.alpha.-(prop-1-ynyl)-estra-4 9-dien-3-one) is the first potent **antiprogestin** in medical use. Acting reversibly at the molecular level of receptor binding, RU 486 blocks progesterone action and allows endocrine functions to return quickly to normal after its use. However, target cells dynamics that depend upon a continuity of progesterone action will be irreversibly disrupted. In normal women RU 486 acts during the luteal phase in the endometrium, provoking **bleeding**, and also decreases LH secretion which results in luteolysis. In pregnant women, if affects the decidual, increases myometrial contractility and ripening of the cervix, and ultimately leads to termination of pregnancy. Detachment of the trophoblast leads to a fall in chronic gonadotrophin. Clinical studies indicate that RU 486 can be a very efficient agent for the termination of early pregnancy, and as a postcoital **menstrual** regulator. The failures observed when RU 486 is given alone may be overcome by the addional use of oxytocics. A small amount of prostaglandin given at the end of RU 486 treatment gives satisfactory results at up to 8 weeks of amenorrhea. Treatment with RU 486 is short term, and apparently has no significant side-effects despite the compound's antiglucocorticosteroid activity.

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